REMARKS

Claims 10, 13-15, 39-50, and 72-84 are pending in the application. Claims 1-9, 11-12, 16-38, and 51-72 have been canceled without prejudice or disclaimer as to the claimed subject matter pursuant to the restriction requirement or otherwise solely to expedite prosecution of the present application. Applicants reserve the right to pursue canceled subject matter in one or more continuation or divisional applications, as appropriate.

Rejections under 35 U.S.C. §112, First Paragraph, Enablement

The rejection of claims 10, 13-15, 39-50, and 72-76 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, was maintained. Applicants traverse this rejection for the reasons set forth below.

In order to establish a *prima facie* case of non-enablement, the examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. See In re Wright, 999 F.2d 1557, 1561-562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement. In re Morehouse, 545 F.2d 162, 165, 192 USPQ 29, 32 (CCPA 1976). Further, even a broad allegation that the disclosure is speculative, coupled with a recitation of various difficulties which might be

encountered in practice, is not sufficient basis for requiring proof of operability. In re Chilowsky, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956).

In the present case, Applicants respectfully submit that the examiner has not provided acceptable evidence that the claimed invention is inconsistent with enablement. At best, the examiner has made broad allegations that the disclosure is speculative and recited various difficulties which might be encountered in practice of the invention. This is not a sufficient evidentiary basis for requiring proof of enablement and a shifting of the burden of proof to appellant. For example, on page 3, line 2 to 9 of the Office Action, the examiner alleges that antisense therapies in general fail to provide any therapeutic efficacy. Specifically, the examiner alleges as follows (emphasis added):

> It is noted that many anti-sense therapies which appear to be promising using transfection in vitro, **fail to provide any therapeutic efficacy** when administered in vivo. Dar and Huang (Molecular Pharmaceutics, 2006, Vol. 3, pp. 2805-2809) teach that antisense therapy is hindered by poor stability in physiological fluids and limited intracellular uptake (abstract). In an article published eight years after the year of the instant filing, Sundaram et al (Nucleic Acids Research, 2007, Vol. 35, pp. 4396-4408) teach that despite the conceptual simplicity of the antisense approach, utilization of antisense is impaired by poor cellular entry and rapid degradation (page 4396, second column, first full paragraph).

The reasons articulated by the Examiner pertain to the general field of antisense therapy and not to the invention itself - i.e., the use of AAH antisense sequences to inhibit tumor growth. Further, the references relied on the examiner -- Dar *et al.* (Molecular Pharmaceutics, 2006, Vol. 3, pp. 2805-2809) ("Dar") and Sundaram *et al.* (Nucleic Acids Research, 2007, Vol. 35, pp. 4396-4408) ("Sundaram") -- do not support the argument that anti-sense therapies "fail to provide any therapeutic efficacy." Applicants submit that these statements mischaracterize the teachings of Dar and Sundaram. First, Dar discloses a new targeted delivery system for anti-sense oligionucleotides that addresses known issues that have been associated with their use. That is, Dar is proposing a solution to maximize the efficacy of anti-sense oligionucleotides. Dar does not teach that anti-sense oligionucleotides therapies "fail to provide any therapeutic efficacy."

The examiner cited a passage in Sundaram that also acknowledges known issues that have been associated with the use of anti-sense oligionucleotides. Again, this is a mischaracterization of the teachings of Sundaram, which provides a case for the need for the rationale design of carriers for "enhanced" oligonucleotide delivery.[1/] Accordingly, this reference also fails to support the examiner's argument that anti-sense therapies "fail to provide any therapeutic efficacy." Indeed, in that same paragraph referenced by the examiner Sundaram goes on to teach that various types of carriers are used for delivery of anti-sense oligonucleotides.

Unlike the problems addressed in Dar and Sundaram, the present invention was not intended to provide, nor does it claim, a particularly new way or new dosage amount for antisense therapy. The specification provides ample guidance on how, and in what amounts, to administer the antisense molecules, in a manner which allows the clinician to use her/his judgment under the particular circumstances of the patient. Such judgments are not deemed to require undue experimentation under the patent law. The Examiner asserts that major technical hurdles pertaining to stability of the administered nucleic acid *in vivo* and uptake of an adequate amount of the administered nucleic acid still remain as problems seven years after the priority date of the instant application. Although in some cases, details pertaining to stability and uptake of nucleic acids may need to be resolved, Applicants submit that those details do not rise to the level of undue experimentation or unpredictability once the target sequence (in this case, AAH) has been identified. The art at and before the time of filing of this application together with the disclosure of the originally-filed specification was sufficient to fulfill the requirements of § 112.

For instance, in 1998, Isis Pharmaceuticals received approval from the Food and Drug Administration (FDA) to market and distribute Vitravene® (fomivirsen sodium), an antisense oligonucleotide, which is administered as naked DNA, to treat cytomegalovirus retinitis in AIDS patients (see Patil et al. DNA-Based Therapeutics and DNA Delivery Systems: A Comprehensive Review. The AAPS Journal 2005; 7(1) Article 9, pp.E61-E77; courtesy copy enclosed). Patil is provided as evidence of a 1998 approval of an antisense oligonucleotide.

1/ Sundaram at Abstract.

Further, again, while Patil acknowledges the known issues with respect to the in vivo administration of antisense oligonucleotides, Patil does not support examiner's argument that anti-sense oligionucleotides therapies "fail to provide any therapeutic efficacy." With respect to anti-sense oligionucleotide therapies, Patil on page E66 teaches that that anti-sense oligionucleotides given the names MG98 and ISIS 5132 are in clinical trials for cancer; ISIS 2302 is being investigated for ulcerative colitis; Affinitak is in Phase III for non-small cell lung cancer; Alicaforsen is in Phase III for Crohn's disease; and Genasense in Phase II from combination treatment for several cancers.

Applicants submit the following references as evidence that the *in vivo* administration and efficacy of antisense therapies was established in the art at and before the time of filing of this application:

1: Avgeropoulos *et al.*, New treatment strategies for malignant gliomas. Oncologist. 1999;4(3):209-24. ("Avgeropoulos 1999").

2: Galderisi *et al.*, Antisense oligonucleotides as therapeutic agents. J Cell Physiol. 1999 Nov;181(2):251-7. ("Galderisi 1999").

3: Cotter *et al.* Antisense therapy for lymphomas. Hematol Oncol. 1997 Feb;15(1):3-11. Review. ("Cotter 1997").

4. Nemunaitis *et al.*, Phase I evaluation of ISIS 3521, an antisense oligodeoxynucleotide to protein kinase C-alpha, in patients with advanced cancer. J Clin Oncol. 1999 Nov; 17(11): 3586-95. ("Nemunaitis 1999").

Cotter 1997, for example teaches that "both in vitro and in vivo efficacy has been established" for anti-sense oligonucleotides (AO), even though anti-sense uptake into the cell is an issue that should be improved.[2/] This includes in vivo efficacy of antisense molecules targeting oncogenes in hematological malignancy.[3/] Further, Cotter 1997 at page 9, last paragraph teaches that AO infusions prolong the bioavailability of the molecule and increase steady-state levels.

[2/] Cotter 1997 at page 9.

[3/] Cotter 1997 at page 96, last full paragraph.

Galdersi 1999 teaches that several clinical studies demonstrated the safety and efficacy of anti-sense oligonucleotides. These studies are summarized by Galdersi 1999 as follows: [4/]

- "Clinical response was observed in some patients suffering from ovarian cancer who were treated with antisense targeted against the gene encoding for the protein kinase C-alpha."
- "Some hematological diseases treated with antisense oligos targeted against the bcr/abl and the bcl2 mRNAs have shown promising clinical response."
- "Antisense therapy has been useful in the treatment of cardiovascular disorders such as restenosis after angioplasty, vascular bypass graft occlusion, and transplant coronary vasculopathy."
- "Antisense oligonucleotides also have shown promise as antiviral agents. Several investigators are performing trials with oligonucleotides targeted against the human immunodeficiency virus-1 (HIV-1) and hepatitis viruses."
- "Phosphorothioate antisense oligonucleotides now have reached phase I and II in clinical trials for the treatment of cancer and viral infections, so far demonstrating an acceptable safety and pharmacokinetic profile for continuing their development."

Galdersi 1999 acknowledges that the continued optimization of oligonucleotide drug properties are important medicinal chemistry objectives. This, however, does not take away from the successes and established efficacy of antisense therapies that was established in the art prior to the filing of this application and summarized above.

Avgeropoulos 1999 teaches that ISIS 3521 is an antisense oligonucleotide that binds to PKC mRNA and is the subject of an ongoing phase II trial for the treatment of recurrent malignant glioma.[5/] This reference discusses the hurdles associated with the systemic administration of antisense oligonucleotides, but states that continuous i.v. infusion is an

[4/] Galdersi 1999 at Abstract.

[5/] Avgeropoulos 1999 at page 214, paragraph spanning the left and right columns.

appropriate route of administration to achieve "sufficient and sustained delivery of antisense oligonucleotides."[6/] This point further supports the teaching of Cotter 1997, which teaches that antisense oligonucleotides infusions prolong the bioavailability of the molecule and increase steady-state levels.[7/]

Nemunaitis 1999 summarized the Phase I evaluation of an antisense oligonucleotide. In short, no dose-limiting toxicity of the antisense molecule was identified, and clinical activity was observed.[8/] In the study, thirty-six patients with advanced cancer received 99 cycles of the antisense molecule (0.15 to 6.0 mg/kg/d) as a 2-hour intravenous infusion administered three times per week for 3 consecutive weeks and repeated every 4 weeks.[9/] Ten patients showed stabilization of the cancer at the 2-month assessment.[10/]

In view of the above, applicants submit that techniques for the *in vivo*, systemic delivery of antisense molecules for the treatment of cancer were established and practiced in the art prior to the filing date of this application. The arguments set forth by the examiner and the discussion in the references of Dar and Sundaram cited by the examiner speak to the need to further optimize the delivery of antisense oligonucleotides in order to achieve maximum efficacy. In this sense, the stability of the oligonucleotides and their cellular uptake are to important factors for the optimization of anti-sense therapies. Patent law, however, does not require maximum efficacy/optimization to be achieved in order to meet the enablement requirement.

As presented above, while Dar and Sundaram provide commentary on the need to optimize or enhance antisense therapies, these references is no way demonstrate that antisense therapies are without clinical efficacy. The clinical safety and efficacy of antisense oligonucleotides was established by the filing date of this application, as is summarize in the references discussed above.

6/ Avgeropoulos 1999 at page 214, first full paragraph.

7/ Cotter 1997 at page 9, last paragraph.

8/ Nemunaitis 1999 at Abstract.

9/ Nemunaitis 1999 at Abstract.

10/ Nemunaitis 1999 at page 3591, right column.

The rejection further states that the specification does not provide adequate disclosure of "...what comprises a therapeutically effective amount of the complementary sequences of the claims." Applicants respectfully disagree. The specification states at page 15, lines 8-10, that while dosages must account for individual variation of the subject's physical characteristics, a general dosage for intravenous (i.v.) administration of nucleic acids is "10^6 to 10^{22} copies of the nucleic acid molecule." As above, Avgeropoulos 1999 and Cotter 1997, support the applicants contention that i.v. infusion is an appropriate route of administration to achieve "sufficient and sustained delivery of antisense oligonucleotides,"[11/] or alternatively, "prolong the bioavailability of the molecule and increase steady-state levels."[12/]

For all of the foregoing reasons, Applicants submit that the rejection of the pending claims should be withdrawn.

[11/] Avgeropoulos 1999 at page 214, first full paragraph.

[12/] Cotter 1997 at page 9, last paragraph.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If the Examiner believes any issues remain that could be resolved by a telephone conference, she is invited to contact the undersigned at the number listed below.

Respectfully submitted,

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